# Ethylene Glycol Kinetics in Pregnant Rats: Differences Between Slow and Fast Dose-Rate Exposures

**E W Carney[1], A B Liberacki[1], B Tornesi[1], KK Weitz[2], TL Luders[2] and R A Corley[2], [1]The Dow Chemical Company, Midland, Michigan; [2]Pacific Northwest National Laboratories, Richland, WA.**

## ABSTRACT

**Large bolus doses of ethylene glycol (EG) are developmentally toxic in rodents. However, human occupational and consumer exposures typically involve low doses and slow dose-rates (e.g. dermal or inhalation). This study examined the impact of dose-rate on maternal and embryonic kinetics of EG and its metabolites. Pregnant CD rats were dosed from gestation days (GD) 6-16 with 1000 or 2000 mg/kg/day of EG given either as a daily subcutaneous (SC) bolus injection (fast dose-rate) or a constant rate of infusion (slow dose-rate) via an implanted pump. Rats were also dosed by oral gavage (fast dose-rate) on GD 11 at either 100 or 1000 mg/kg. EG and its developmentally toxic metabolite, glycolic acid (GA) were determined in maternal blood samples on GD 7-15 in the SC bolus injection and continuous infusion study. Detailed analysis of the kinetics of EG, GA and oxalic acid (OX) were also determined in maternal blood, urine and kidneys, as well as conceptus fluids and embryos on GD 11-12 for the oral gavage and SC infusion studies. EG levels were similar in maternal blood vs. maternal tissues and conceptuses within a given treatment group, while GA levels were consistently higher in tissues than maternal blood. OX levels at all dose levels were variable but similar to control levels in all samples regardless of dose. Blood levels of EG and GA were similar following the two bolus administration routes. However, peak blood levels for both EG and GA were consistently higher (~5-fold for EG and ~50-fold for GA) following bolus oral and SC dosing than following constant rate SC infusion at comparable total dose levels. The lower levels of GA observed in the slow dose-rate group corresponded with the low toxicity characteristic of slow dose-rate administration of EG, as shown in previous studies. Therefore, bolus dosing with EG appears to significantly overestimate the risk of typical occupational and consumer exposures to EG.** ***Funded by the American Chemistry Council, Arlington, VA.***

## BACKGROUND

- **Ethylene glycol (EG) is a high production volume chemical that is teratogenic (e.g. axial skeleton defects) in rodents given large oral bolus doses, but shows little to no developmentally toxicity for non-bolus exposures (e.g., dermal).**
- **The proximate toxicant is EG's metabolite, Glycolic Acid (GA).**
- **GA kinetics become saturated at doses causing developmental toxicity.**
- **Proposed threshold for developmental toxicity is 2 mM GA in maternal blood.**
- **Hypothesize that EG developmental toxicity is a high dose, high dose-rate phenomenon relevant only to oral bolus ingestion, but is unlikely to occur for typical human exposures (e.g., low-dose dermal and/or inhalation).**

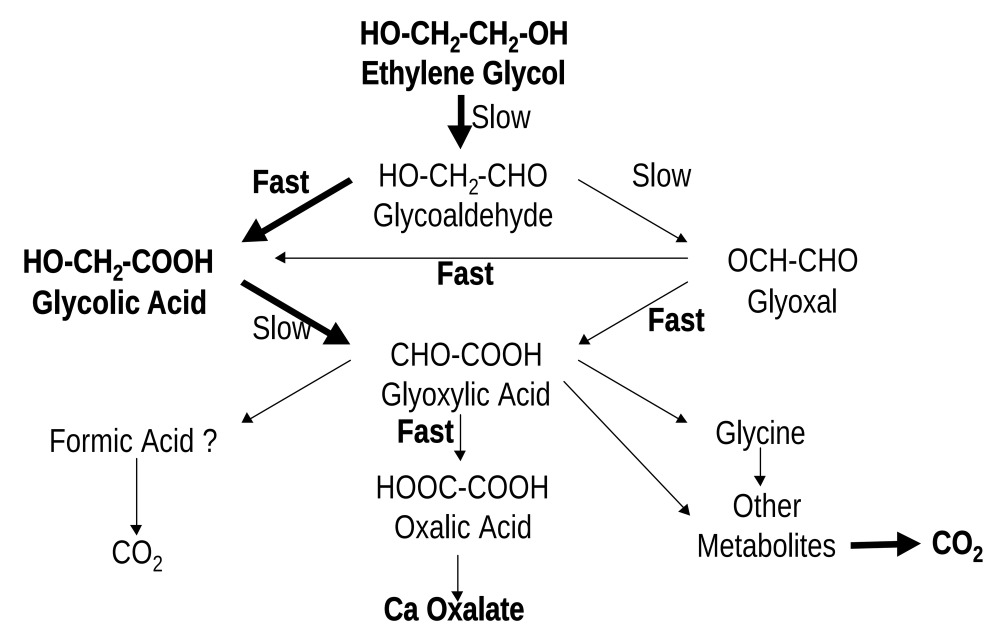



Fig. 1. Metabolism of ethylene glycol.

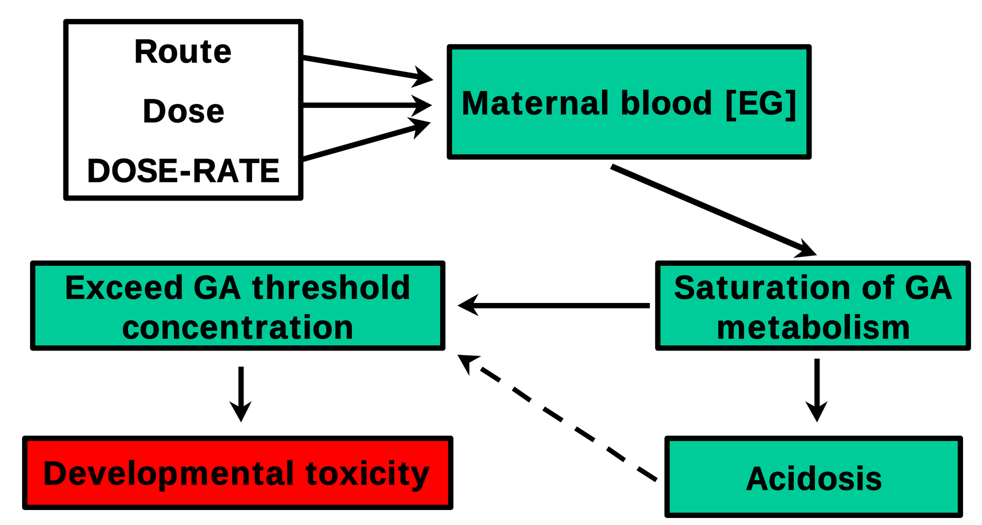


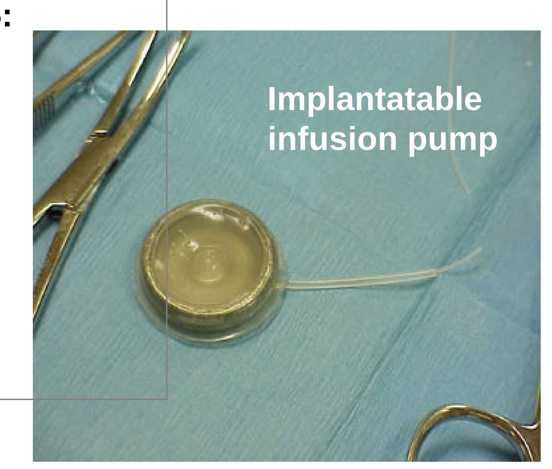

Fig. 2. Proposed mode of action for ethylene glycol developmental toxicity.

## STUDY DESIGN

**Continuous subcutaneous infusion of EG on gd 6-15:**
1000 and 2000 mg/kg/d:
Steady-state blood, kidney, urine, EEF & embryo levels of EG, GA and OX on gd 11 &12.
Fetal evaluation gd 21.

**Daily bolus subcutaneous injections of EG on gd 6-15:**
1000 and 2000 mg/kg/d
3-hr post-dosing blood levels of EG & GA on gd 7, 9,12 & 15.
Fetal evaluation gd 21.

**Single bolus oral gavage of EG on gd 11:**
100 and 1000 mg/kg
24-hr kinetics of EG, GA & OX in blood, kidney, urine, EEF & embryos




## RESULTS

### GD 11GAVAGE DOSING

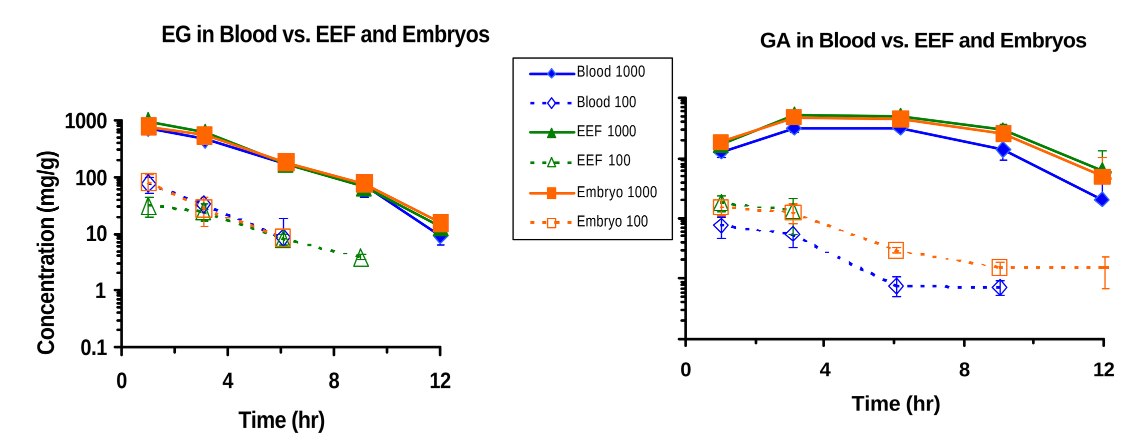



Fig. 3. Time-course of EG and GA in maternal blood, exocoelomic/amniotic fluid (EEF) and embryo after a gavage dose of 100 or 1000 mg/kg EG.

### GD 11GAVAGE DOSING

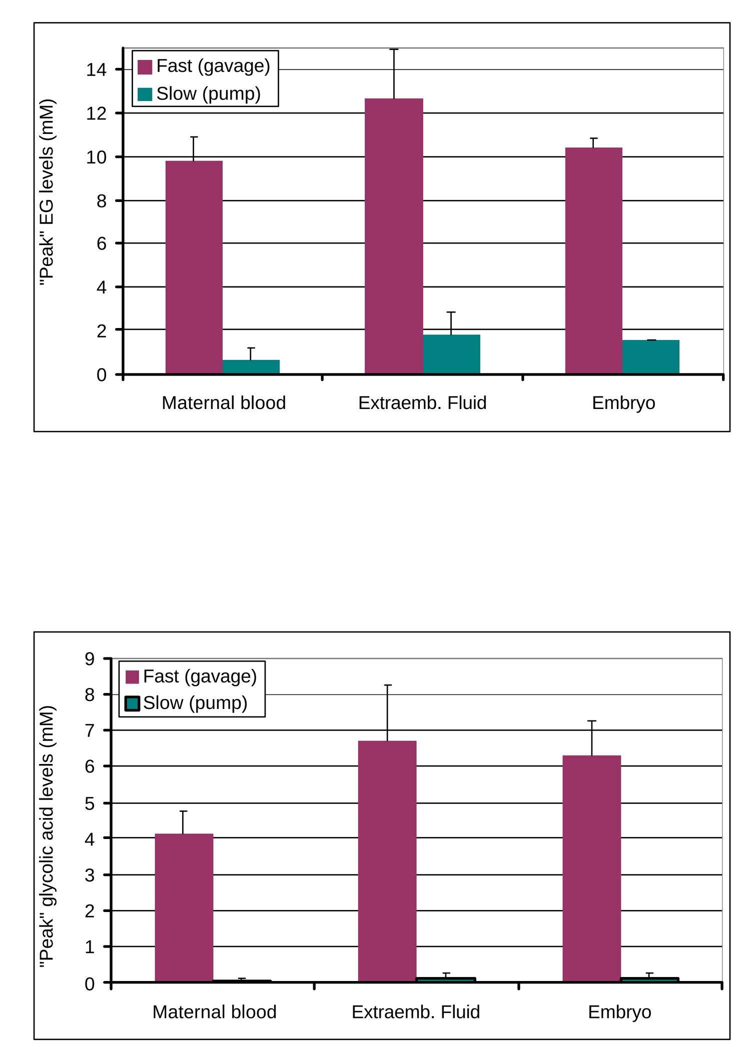



Fig. 4. Levels of EG (top) and GA (bottom) after 1000 mg/kg dose of EG given as a bolus or infusion.
**Bolus administration results in 65x (blood), 53x (extraemb. Fluid), or 48x (embryo)-fold higher GA levels than same dose given slowly.**

### GD 6-15 DAILY SC BOLUS VS. CONTINUOUS SC INFUSION

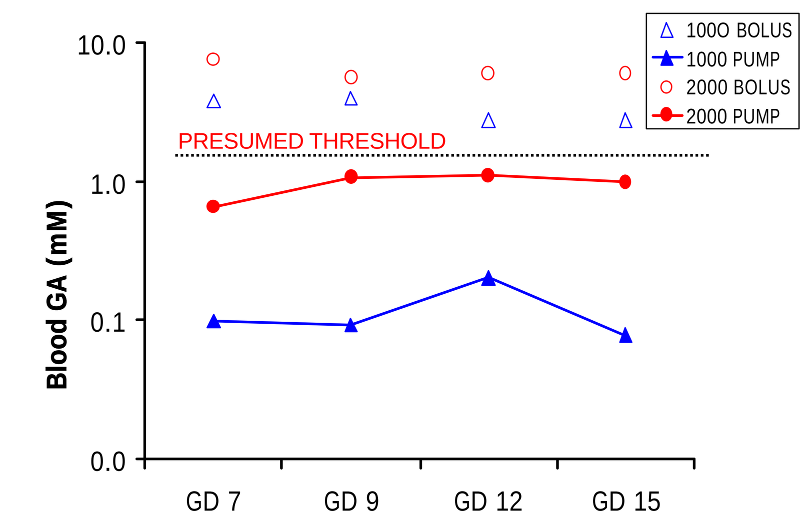



Fig. 5. Maternal blood GA levels: bolus vs. infusion pump

| | Bolus 2000 (mg/kg/d) | Bolus 1000 (mg/kg/d) | Infusion 2000 (mg/kg/d) | Infusion 1000 (mg/kg/d) |
|---|---|---|---|---|
| Decreased fetal body weight | Yes | Slight | No | No |
| No. skeletal malformations increased | 12 | 2 | 0 | 0 |
| No. skeletal variations increased | 11 | 2 | 0 | 0 |

Table 1. Fetal evaluation on GD 21 after dosing at a fast dose-rate (daily SC injection) or slow dose-rate (continuous infusion) from GD 6-15.

## CONCLUSIONS

**1) Bolus dosing with EG leads to saturation of GA kinetics, leading to ~ 50x increase in embryonic exposure to the proximate toxicant.**

**2) Even continuous exposure to 1 mM blood GA was without effect, supporting a threshold estimate of at least 2 mM maternal blood GA.**

**3) Embryo GA consistently tracks maternal blood GA by factor of ~ 2x, facilitating use of maternal blood GA as a key internal dose metric.**